PATENT
REISSUE APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of:

Raffa, *et al.*

U.S. Patent No. **5,336,691**

Issue Date: **August 9, 1994**

Application No. **07/974,865**

Filed: **November 10, 1992**

Reissue Application Filed: **January 20, 2004**

Reissue Application No. 10/761,096

For: **COMPOSITION COMPRISING A TRAMADOL MATERIAL AND ACETAMINOPHEN AND ITS USE**

Examiner: **William R.A. Jarvis**

Art Unit: **1205**

8/4/04
Scan
Washington
TPRG, TC 1600

PROTEST UNDER 37 CFR 1.291 (a)

Mail Stop BOX DAC
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 CFR 1.291 and MPEP §1900, protest is hereby made against the reissue application of US Patent No. 5,336,691 (the '691 patent), filed November 10, 1992, and assigned Application No. 07/974,865. The reissue application has been assigned Application No. 10/761,096. Notice of the reissue application was published in the Office Gazette on June 8,

I hereby certify that this correspondence is being deposited in duplicate with the United States Postal Service as First Class Mail in an envelope addressed to: Mail Stop Box DAC, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, and to the prosecuting attorney of record: Joseph Lucci, Woodcock Washburn LLP, One Liberty Place – 46th Floor, Philadelphia, PA 19103, on August 6, 2004.

William L. Warren, Reg. No. 36,714

2004. This protest is being filed within two months of the publication date. The required fees for this Protest should be charged to Deposit Account No. 19-5029.

REMARKS

The pending claims 6 and 15-66 in the reissue application (Appendix A) are unpatentable as being anticipated, inherently anticipated, and obvious in view of either U.S. Patent No. 3,652,589 or U.S. Patent No. 3,830,934 (the Flick patents) teaching combinations of tramadol with p-acetamino phenol, and tramadol with phenacetin, for synergistic pain relief.

Enclosed is PTO form 1449 (Appendix B), listing the references relied upon. Copies of the references are also enclosed. A concise explanation of the relevance of each reference follows.

A. U.S. Patent No. 5,336,691 (the '691 patent) and Its Reissue Application

The '691 patent was filed on November 10, 1992 and issued on August 9, 1994. It is directed to a composition comprising a tramadol material and acetaminophen for the treatment of pain and tussive conditions. Patentee discloses that the analgesic effect of the composition is synergistic, and provides a wide range of synergistic weight ratios of tramadol to acetaminophen from about 1:1 to 1:1600. The patent includes 15 claims with one independent claim 1 that is directed to "[A] pharmaceutical composition comprising a tramadol material and acetaminophen, wherein the ratio of the tramadol material to acetaminophen is a weight ratio from about 1:1 to about 1:1600." Claims 2 – 8, depending upon claim 1, further define the tramadol material as being tramadol hydrochloride and racemic (claim 2-3), and narrow the weight ratio as being "about 1:1" (claim 4), "from about 1:5 to about 1:1600" (claim 5), "about 1:5" (claim 6), "from about 1:19 to about 1:800" (claim 7) or "from about 1:19 to about 1:50"

(claim 8). Claims 9-14, depending upon claim 1, claim that the pharmaceutical composition further comprises "a pharmaceutical acceptable carrier" (claim 9), "a decongestant or bronchodilator" (claim 10), "an antitussive" (claim 11), "an antihistamine or a non-sedating antihistamine" (claim 12), "a muscle relaxant" (claim 13), or "a sleep aid" (claim 14). Claim 15 is directed to "[A] method for treating a pain in a mammal comprising an administration to the mammal an effective amount of the pharmaceutical composition of claim 1."

A reissue application of the '691 patent was filed on January 20, 2004. In the reissue application, patentee requested cancellation of claims 1-5 and 7-14; amendment of claims 6 and 15 and entry of new claims 16-66. A listing of pending claims 6, 15 and 16-66 of the reissue application is provided as Appendix A herewith. Amended claims 6 and 15 are directed to a composition and method of use, respectively, "comprising a tramadol material and acetaminophen" in a weight ratio of "about 1:5". Pending claims 16-66 recite compositions and methods of use with "an active ingredient that consists essentially of tramadol and acetaminophen" in various ratios and with various other dependent claim limitations similar to those described above.

Although Applicants were aware that the '691 patent is the subject of concurrent litigation (*Ortho-McNeil Pharmaceutical, Inc. v. Kali Laboratories, Inc.*, Civ. A. No. 02-5707 (JCL), U.S. District Court for the District of New Jersey; and now also *Ortho-McNeil Pharmaceutical, Inc. v. Teva Pharmaceutical Industries Ltd and Teva Pharmaceuticals USA, Inc.*, Civ. A. No. 04-886 (HAA), U.S. District Court for the District of New Jersey), Applicants requested that action not be stayed in the requested reissue application.

B. Discussion of the Prior Art References

1. USPN 3,652,589 (the '589 reference patent) to Flick et al.

The '589 reference patent to Flick et al. discloses a class of cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring, which are useful as analgesic drugs (Col. 1, lines 15-17). The compound (1RS, 2RS)-[(dimethylamino)-methyl]-1-(3-methoxyphenyl) cyclohexanol, commonly known as tramadol, and the process of making it are specifically disclosed in the '591 reference patent (see Applicant's admission in Col. 1, lines 14-19 of the '691 patent). The '589 reference patent has been incorporated by reference in the '691 patent (Col. 3, lines 21-24 of the '691 patent).

The '589 reference patent discloses that tramadol has therapeutic value and synergistic effect when combined with phenacetin:

> "The compounds according to the present invention have also proven to be of considerable therapeutic value when used in combination with other therapeutically active agents whereby frequently a synergistic effect is observed. Especially valuable combinations are those with other analgesics such as with acetylsalicyclic acid, phenacetin, or the like...." (emphasis added, Col. 12, lines 45-52 of the '589 reference patent).

The '589 reference patent also provides an example disclosing a combination of tramadol with p-acetamino phenol in a 1:10 ratio:

> "Example 23
>
> Tablets which are composed as follows are compared in the conventional manner:
>
> 25 mg. of the hydrochrloride of racemic 1(e)-(m-methoxy phenyl – 2(e) – dimethylamino methyl cyclohexane-1(a)-ol,

30 mg. of pentobarbital sodium,

250 mg. of ethoxy benzamide

250 mg. of p-acetamino phenol" (emphasis added, Col 12, lines 65-75)

The '589 reference patent was a continuation-in-part of an abandoned application Serial No. 357,024, which was filed on March 30, 1964. The '589 reference patent was filed on July 27, 1967 and issued on March 28, 1972. The specification of the '589 reference patent was incorporated by reference into the '691 patent specification and the present reissue application.

2. **USPN 3,830,934 (the '934 reference patent) to Flick et al.**

The '934 reference patent was filed as a divisional application of the '589 reference patent. It was filed on January 13, 1972 and issued on August 20, 1974. The '934 reference patent is directed to a method of providing analgesic and antitussive effects by administering an effective dose of a pharmaceutical composition comprising, as an essential agent, the compounds disclosed and claimed in the '589 reference patent, including tramadol.

As a divisional application, the '934 reference patent specification is identical to the '589 reference patent specification. Therefore, the '934 reference patent also discloses pharmaceutical formulations including:

1) tramadol and phenacetin (Col. 12, lines 35-41); and

2) tramadol and p-acetamino phenol [*sic*] in a ratio of 1:10 (typographical error of "p-acetamina phenol" to "p-acetamino phenol" corrected, Col. 12, lines 56-61).

Therefore, both the Flick patents disclose that compositions including tramadol with the analgesics phenacetin or p-acetamino phenol provide a therapeutically synergistic effect for treating pain and tussive conditions.

3. **Hardman et al., GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 5th Ed., p. 656-659 (1990)**

Acetaminophen is the only major active metabolite of phenacetin. Phenacetin, itself a chemical derivative of para-aminophenol, was introduced into therapy in 1887 and was extensively employed in analgesic mixtures until it was implicated in analgesic-abuse nephropathy. Acetaminophen was first used in medicine in 1893, and has gained popularity since 1949 after it was recognized as the major active metabolite of phenacetin.

4. **FDA, Prescription and Over-the-Counter Products Containing Phenacetin, Federal Register, 47 FR 34636 (1982)**

The U.S. Government provided official notice in the Federal Register in 1982 that phenacetin, the metabolic precursor of acetaminophen, was mandated by the FDA to be withdrawn from the U.S. market and replaced with acetaminophen or aspirin on a milligram for milligram basis for phenacetin-containing products because of its renal toxicity. The reformulation of phenacetin-containing products with acetaminophen or aspirin was required by the FDA to be completed by August 10, 1983.

C. The Claims 6 and 15-66 In The Reissue Application Are Unpatentable As Being Anticipated By The '589 Reference Patent And The '934 Reference Patent to Flick et al. ("the Flick Patents").

1. **Claims 6 and 15 are anticipated by the Flick Patents.**

Pending claims 6 and 15 are directed to a composition and method of use, respectively, "comprising a tramadol material and acetaminophen" in a weight ratio of "about 1:5". Claims 6 and 15 are anticipated by the Flick Patents. "For a claim to be invalid on anticipation grounds, a single prior art reference must either expressly or inherently disclose all

limitations of the claimed invention in a way that enables one skilled in the art to make the anticipating subject matter." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). The Flick patents constitute prior art to the '691 patent because they were filed and issued sufficiently before the '691 patent was filed. *See* 35 U.S.C. §102 (a),(b) & (e).

As discussed above, the Flick patents disclose in Example 23 analgesic compositions including tramadol with p-acetamino phenol in a weight ratio of 1:10, and disclose methods of providing synergistic analgesic effects to a patient by administration of such combinations.

Acetaminophen is commercially available in the U.S. from the assignee of the present re-issue application McNeil Lab, Inc. under the tradename TYLENOL®, and is also commonly known by the synonym p-acetaminophenol, among others. *See* National Institute for Occupational Safety and Health, Registry of Toxic Effects of Chemical Substances No. AE4200000, Synonyms, 2003 (www.cdc.gov/niosh/rtecs/ae401640.html) (Appendix C). There is no chemical difference between the compounds described as "p-acetaminophenol" and "p-acetamino phenol" under generally accepted rules of chemical nomenclature, e.g. as provided by the International Union of Pure and Applied Chemistry (IUPAC). Therefore, the Flick patents disclose in Example 23 analgesic compositions comprising tramadol and acetaminophen in a ration of 1:10.

The present re-issue Applicants offer claims 6 and 15 directed to a composition and method of use, respectively, "comprising a tramadol material and acetaminophen" in a weight ratio of "about 1:5". The term "about" has not been defined in the specification. However, the Flick patents teach compositions and methods of use of tramadol and p-acetamino phenol, also known as acetaminophen, in a weight ratio of 1:10. To the extent that the term "about 1:5" in

claims 6 and 15 reads on the 1:10 ratio of the same ingredients taught in the Flick patents, the claims are clearly anticipated.

2. **Claims 6 and 15-66 are inherently anticipated by the Flick Patents.**

Pending claims 6 and 15 are directed to a composition and method of use, respectively, "comprising a tramadol material and acetaminophen" in a weight ratio of "about 1:5". Pending claims 16-66 recite compositions and methods of use with "an active ingredient that consists essentially of tramadol and acetaminophen" in various ratios and with various other dependent claim limitations. Claims 6 and 15-66 are inherently anticipated by the Flick patents. As discussed above, the Flick patents disclose that tramadol has therapeutic value and synergistic effect when combined with phenacetin. Phenacetin, itself a chemical derivative of para-aminophenol, was introduced into therapy in 1887 and was extensively employed in analgesic mixtures until it was implicated in analgesic-abuse nephropathy. Acetaminophen was first used in medicine in 1893, and has gained popularity since 1949 after it was recognized as the major active metabolite of phenacetin. In 1982, the FDA mandated that phenacetin be withdrawn from the U.S. market and replaced with acetaminophen or aspirin on a milligram for milligram basis for any phenacetin-containing products because of its renal toxicity. *See* Federal Register, 47 FR 34636, 9 (1982).

Therefore, it has long been established that phenacetin is the major metabolic precursor of acetaminophen. The Flick patents teaching of synergistic combinations of tramadol and phenacetin inherently anticipates a composition "comprising" the combination of tramadol and acetaminophen as in pending claim 6, and its use for treating pain and obtaining synergistic effects as in pending claim 15.

Pending claims 16-66 recite compositions and methods of use with a combination "consisting essentially of' a combination of tramadol and acetaminophen in various ratios. There is no written support or evidentiary indication that Applicants of the '691 patent possessed an invention "consisting essentially of" a combination of tramadol and acetaminophen that was uniquely synergistic over combinations which included other active ingredients. Furthermore, no patentable weight can be given to the relative ratios in the pending claims where no evidence has been offered to demonstrate an unexpectedly synergistic effect. Therefore, all of the claims in the present re-issue application are invalid as inherently anticipated by the Flick patents.

In *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), the prior art '233 patent covered the antihistamine loratadine. Claims 1 and 3 of the '716 patent covered a metabolite of loratadine, descarboethoxyloratadine (DCL), which was inevitably formed from loratadine in the human body. 339 F.3d at 1378. The court found that while the '233 patent did not expressly disclose DCL and did not refer to metabolites of loratadine, the '233 patent still anticipated claims 1 and 3 of the '716 patent. *Id.* at 1380. The court reasoned that a prior art reference may anticipate without disclosing a particular feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Id.*

Further, the court recognized that "patent law precedent does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed.... Patent law nonetheless establishes that a prior art reference which expressly or inherently contains each and every limitation of the claimed subject matter anticipates and invalidates." *Id.* at 1378. The court explained that "the record shows that the metabolite of the prior art loratadine is the same compound as the claimed invention..... a patient ingesting loratadine would necessarily

metabolize that compound to DCL..... A prior art reference showing administration of loratadine to a patient anticipates claims 1 and 3." *Id.* at 1380. Therefore, the disclosure in the Flick patents of a synergistic combination of phenacetin with tramadol inherently anticipates the presently claimed combination of phenacetin's major active metabolite acetaminophen with tramadol.

Another similar case is *In re Omeprazole Patent Litigation*, 2001 U.S. Dist. Lexis 7103 (S.D.N.Y. 2001) where the court recognized that since omeprazole is naturally converted into sulphenamides in the human body, a prior omeprazole patent inherently anticipated claims made in a later sulphenamides patent. Similarly, in *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 340 (S.D.N.Y. 2002), there was no dispute that the 6-hydroxy-metabolite is one of metabolites that buspirone naturally produces in the human body and is itself active, and the court found that the '365 patent was invalid because "the prior use of buspirone inherently anticipated the uses of buspirone that favor production of the 6-hydroxy-metabolite." *Id.* at 361.

The present case is clearly distinguished from in *Marion Merrell Dow, Inc. v. Geneva Pharmaceuticals, Inc.*, 877 F. Supp. 531 (D. Colorado, 1994), where the presursor compound was metabolized in the patient's body into two major metabolites, one of them being TAM, the subject of a later patent claim. The court ruled that Geneva did not present sufficiently material facts to rule for a summary judgment of invalidity that terfenadine described in the prior art '217 patent inevitably or invariably resulted in the formation of TAM. *Id* at 536. In the present case, however, acetaminophen is inevitably and invariably the only major metabolite of phenacetin (Hardman et al., GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 5th Ed., p. 656-659 (1990), and therefore, the Flick patents' teaching of a synergistic combination of

phenacetin and tramadol inherently anticipates the claimed synergistic combination of acetaminophen and tramadol.

Inherent anticipation has also been found in many other relevant cases. *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1994) (Inherency is not necessarily conterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art); *Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.*, 246 F.3d 1368 (Fed. Cir. 2001) (newly discovered results of known process directed to the same purpose are not patentable because such results are inherent) (citing *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978) (claims to the method of effecting analgesic activity without producing physical dependency by administering a genus of non-additive analgesic compounds were anticipated by a disclosure of a species of that genus that was used as an analgesic)); *Perricone v. Medicis Pharmaceutical Corp.*, 267 F. Supp. 2d 229 (D. Conn. 2003) (although the prior art reference "does not expressly disclose the use of an ascorbyl fatty acid ester for treating or preventing skin sunburn, the topic application of a cream or lotion containing an amount of ascorbyl fatty acid ester disclosed ..... will in its 'normal and usual operation' treat and prevent sunburn." *Id.* at 244).

Regarding the presently claimed compositions "consisting essentially of" a combination of tramadol and acetaminophen, the Flick patents clearly teach compositions containing only the active ingredients tramadol and phenacetin, the inherent precursor of acetaminophen (*See* '589 reference patent, Col. 12, lines 45-50). Additionally, Applicant has not demonstrated possession of an invention having a superior result with the limited combination of tramadol and acetaminophen over the combination of tramadol, p-acetamino phenol and the sleep aid pentobarbital sodium shown in Example 23 of the Flick patent. On the contrary, Applicants

taught that compositions of tramadol and acetaminophen can also contain decongestants, antitussives, antihistamines, muscle relaxers, and sleeping aids, for example. (*See,* '691 patent at Col. 4, lines 9-41, and claims 10-14).

Regarding the presently claimed specific ratios, the court addressed a similar situation in *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342 (Fed. Cir. 1999). The court had to decide whether a patent claiming explicit limitations of ratios for sufficient aeration was anticipated by two prior patents that were not limited to compositions with those ratios. The court found that the prior art anticipated the patent because the prior art inherently produced sufficient aeration in a limited set of circumstances. *Id.* at 1349. The court reasoned that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art." *Id.* at 1346. Therefore, the presently claimed specific ratios of tramadol and acetaminophen are also inherently anticipated by the Flick Patents.

There has been no showing of a statistically significant superior result or unexpected improved synergism in certain ratios over that expected by the prior art. On the contrary, Applicants initially argued to the Patent Office for patentabilty of all compositions in the range of 1:1 to 1:1600 demonstrated by the isobologram without patentable distinction between the ratios.

In the present matter, the Flick patents inherently anticipate the claimed synergistic combination of tramadol and acetaminophen in all of the pending claims 6 and 5-66, because they disclose that the opioid compounds described in the patents, including tramadol, can provide a synergistic effect when combined with other analgesics, specifically referencing

combinations with either phenacetin (acetaminophen precursor) or p-acetamino phenol (acetaminophen).

D. Claims 6 and 15-66 In The Reissue Application Are Unpatentable As Being Obvious In View Of The Flick Patents

Alternatively, all of pending claims 6 and 15-66 in the reissue application are unpatentable as being obvious in view of the Flick patents. It would have been *prima facie* obvious to one skilled in the art to combine tramadol with acetaminophen for the synergistic effect on pain relief as described at the time the '691 patent was filed, in view of the teaching in the Flick patents that combine tramadol with phenacetin or with p-acetamino phenol for the same purpose.

A claim is invalid for obviousness if the differences between the subject matter patented and the prior art are such that the patented subject matter as a whole would have been obvious to a person of ordinary skill in the art. *See* 35 U.S.C. §103. Obviousness is a legal conclusion based on the following factual inquires: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of nonobviousness. *See McNeil-PPC, Inc. v. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003).

The Flick patents clearly teach the combinations of: 1) tramadol with phenacetin; and 2) tramadol with p-acetamino phenol for synergistic pain relief. Acetaminophen was well-known to be the major active metabolite of phenacetin a decade before the '691 patent was filed, and was mandated by the FDA as a replacement option for phenacetin. Also, p-acetamino phenol is

the same compound as acetaminophen. The re-issue application claims a composition "comprising" (claims 6 and 15) and "consisting essentially of" (claims 16-66) a combination of tramadol and acetaminophen for the same purpose, i.e., a synergistic pain relief. There is no evidence to suggest that specifically claimed ratios of tramadol and acetaminophen are unexpectedly synergistic, or to demonstrate possession of an invention whereby the presence of other active ingredients would materially affect the claimed synergy. Therefore, all of the pending reissue claims for compositions and methods of use would have been *prima facie* obvious to a person of ordinary skill in the art at the time the '691 patent was filed.

The synergistic effect of combining tramadol and acetaminophen in various weight ratios is predicted and not unexpected because no evidence is presented that one specific weight ratio is more unexpectedly synergistic than others. Considering the predictability of the invention, obviousness does not require absolute predictability, it only requires a reasonable expectation of obtaining similar properties. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *See, In re Merck & Co.*, 800 F.2d 1090 (Fed. Cir. 1986) (holding that the differences in sedative and anticholinergic effects between prior art and claimed antidepressants were not unexpected).

The Federal Circuit has defined the term "unexpected" results as "superior" results. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). The Flick patents teach a synergistic combinations of: 1) tramadol with phenacetin (acetaminophen precursor); and 2) tramadol with p–acetamino phenol (acetaminophen). In the present reissue application, no statistically significant superior result in any particular range has been demonstrated, nor has any superior

synergism been shown using a composition of only acetaminophen and tramadol over that expected with compositions comprising additional active ingredients.

In *Richardson-Vicks Inc. v. The Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) the court ruled that the plaintiff's patent that combined two ingredients in a single unit dosage for a cough and cold formula was invalid for obviousness. Specifically, the patent claimed the combination of two well-known ingredients, the analgesic ibuoprofen and the decongestant pseudoephedrine, in various ratios. The court found that the difference between the claimed invention and the prior art, i.e. other combined dosage cough and cold products such as CO-TYLENOL®, is that the prior art used acetaminophen or aspirin, instead of ibuprofen in a single unit dosage. *Id.* at 1481. The patentee relied heavily on evidence of analgesic and anti-inflammatory response "synergy" between the ibuprofen and the pseudoephedrine, established by an isobologram method. *Id.* Despite the fact that the evidence of unexpected results based on the mice experiments was dispositive in the PTO, the court considered this evidence irrelevant because "the alleged synergistic property of the patented combination was unknown at the time of Dr. Sunshine's invention." *Id.* at 1482. The court stated that the unexpected results of the claimed invention, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious." *Id.* at 1483-84.

In the present case, the Flick patents teach a synergistic combination of tramadol with phenacetin or p-acetamino phenol. Any unexpectedly synergistic distinctions claimed in the re-issue application between the specific ratios or compositions "consisting essentially of" only tramadol and acetaminophen were not known or appreciated by Applicants at the time of the invention as evidenced by the '691 patent specification and file history. To the contrary, Applicants of the '691 patent taught and argued synergistic combinations of tramadol and

acetaminophen at ratios ranging across the entire isobologram from 1:1 to 1:1600, and when co-formulated with decongestants, antitussives, antihistamines, muscle relaxers, sleep aids and other active ingredients. (Col 4, lines 9-41). As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing." *Chiron Corp. v. Genentech Inc.*, 70 USPQ2d 1321, 1330 (Fed. Cir. 2004). Since no evidence of ratio or exclusive combinatory super-synergistic effects was described in the '691 specification or prior file history, Applicants' claimed invention must be directed only to expected synergistic combinations and methods of use, which are merely obvious over the Flick patents, and therefore unpatentable.

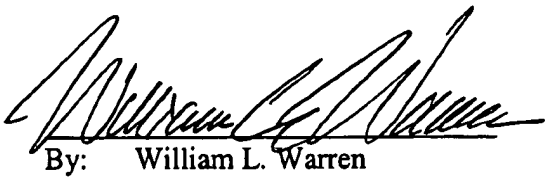
CONCLUSION

Accordingly, the pending claims 6 and 15-66 in the reissue application are unpatentable as being anticipated, inherently anticipated, or obvious in view of the Flick patents teaching combinations of tramadol with p-acetamino phenol, and tramadol with phenacetin, for synergistic pain relief. Because p-acetamino phenol is a synonym for acetaminophen, and acetaminophen is the major active metabolite of phenacetin, it would be reasonable and expected for one skilled in the art at the time to combine acetaminophen with tramadol to provide the claimed synergistic analgesic effect.

For the foregoing reasons, we respectfully protest the above-identified pending reissue application. Please acknowledge receipt of this protest by stamping and returning the attached self-addressed postcard. Please also acknowledge entry of this protest in the reissue application file. The required fees for this Protest should be charged to Deposit Account No. 19-5029. The Examiner is invited to call the undersigned attorney at (404) 853-8081 if the Examiner has any questions in this regard.

Dated this 6th day of August, 2004.

Respectfully submitted,



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This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-5. (canceled)

6. (currently amended) [The pharmaceutical composition of claim 5 wherein the] A pharmaceutical composition comprising a tramadol material and acetaminophen, wherein the ratio of the tramadol material to acetaminophen is a weight ratio [is] of about 1:5.

7-14. (canceled)

15. (currently amended) A method for treating [a] pain in a mammal comprising [an administration] administering to the mammal an effective amount of the pharmaceutical composition of [claim 1] claim 6.

16. (new) A pharmaceutical composition comprising an active ingredient that consists essentially of tramadol and acetaminophen, wherein the ratio of tramadol to acetaminophen is a weight ratio from about 1:1 to about 1:1600.

17. (new) The pharmaceutical composition of claim 16 wherein the tramadol is racemic.

18. (new) The pharmaceutical composition of claim 16 wherein the tramadol is present as its hydrochloride salt.

19. (new) The pharmaceutical composition of claim 18 wherein the tramadol hydrochloride is racemic.

20. (new) The pharmaceutical composition of claim 16 wherein said active ingredient consists essentially of an admixture of said tramadol and said acetaminophen.

"

21. (new) The pharmaceutical composition of claim 16 wherein the weight ratio is about 1:1.

"

22. (new) The pharmaceutical composition of claim 16 wherein the weight ratio is from about 1:5 to about 1:1600.

23. (new) The pharmaceutical composition of claim 16 wherein the weight ratio is about 1:5.

24. (new) The pharmaceutical composition of claim 16 comprising a pharmaceutically acceptable carrier.

25. (new) The pharmaceutical composition of claim 16 that is in the form of a powder.

26. (new) The pharmaceutical composition of claim 16 that is in the form of a capsule.

27. (new) The pharmaceutical composition of claim 16 that is in the form of a tablet.

28. (new) The pharmaceutical composition of claim 16 that is in the form of a suspension.

29. (new) The pharmaceutical composition of claim 16 that is in the form of a solution.

30. (new) A method for treating pain in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 16.

31. (new) A pharmaceutical composition comprising an active ingredient that consists essentially of tramadol and acetaminophen, wherein the ratio of tramadol to acetaminophen is a weight ratio from about 1:5 to about 1:50.

32. (new) The pharmaceutical composition of claim 31 wherein the tramadol is racemic.

33. (new) The pharmaceutical composition of claim 31 wherein the tramadol is present as its hydrochloride salt.

34. (new) The pharmaceutical composition of claim 33 wherein the tramadol hydrochloride is racemic.

35. (new) The pharmaceutical composition of claim 31 wherein said active ingredient consists essentially of an admixture of said tramadol and said acetaminophen.

36. (new) The pharmaceutical composition of claim 31 comprising a pharmaceutically acceptable carrier.

37. (new) The pharmaceutical composition of claim 31 that is in the form of a powder.

38. (new) The pharmaceutical composition of claim 31 that is in the form of a capsule.

39. (new) The pharmaceutical composition of claim 31 that is in the form of a tablet.

40. (new) The pharmaceutical composition of claim 31 that is in the form of a suspension.

41. (new) The pharmaceutical composition of claim 31 that is in the form of a solution.

42. (new) A method for treating pain in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 31.

43. (new) A pharmaceutical composition comprising an active ingredient that consists essentially of tramadol and acetaminophen, wherein the ratio of tramadol to acetaminophen is a weight ratio from about 1:5 to about 1:19.

44. (new) The pharmaceutical composition of claim 43 wherein the tramadol is racemic.

45. (new) The pharmaceutical composition of claim 43 wherein the tramadol is present as its hydrochloride salt.

46. (new) The pharmaceutical composition of claim 45 wherein the tramadol hydrochloride is racemic.

47. (new) The pharmaceutical composition of claim 43 wherein said active ingredient consists essentially of an admixture of said tramadol and said acetaminophen.

48. (new) The pharmaceutical composition of claim 43 comprising a pharmaceutically acceptable carrier.

49. (new) The pharmaceutical composition of claim 43 that is in the form of a powder.

50. (new) The pharmaceutical composition of claim 43 that is in the form of a capsule.

51. (new) The pharmaceutical composition of claim 43 that is in the form of a tablet.

52. (new) The pharmaceutical composition of claim 43 that is in the form of a suspension.

53. (new) The pharmaceutical composition of claim 43 that is in the form of a solution.

54. (new) A method for treating pain in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 43.

55. (new) A pharmaceutical composition comprising an active ingredient that consists essentially of tramadol and acetaminophen, wherein the ratio of tramadol to acetaminophen is a weight ratio from about 1:19 to about 1:50.

56. (new) The pharmaceutical composition of claim 55 wherein the tramadol is racemic.

57. (new) The pharmaceutical composition of claim 55 wherein the tramadol is present as its hydrochloride salt.

58. (new) The pharmaceutical composition of claim 57 wherein the tramadol hydrochloride is racemic.

59. (new) The pharmaceutical composition of claim 55 wherein said active ingredient consists essentially of an admixture of said tramadol and said acetaminophen.

60. (new) The pharmaceutical composition of claim 55 comprising a pharmaceutically acceptable carrier.

61. (new) The pharmaceutical composition of claim 55 that is in the form of a powder.

62. (new) The pharmaceutical composition of claim 55 that is in the form of a capsule.

63. (new) The pharmaceutical composition of claim 55 that is in the form of a tablet.

64. (new) The pharmaceutical composition of claim 55 that is in the form of a suspension.

65. (new) The pharmaceutical composition of claim 55 that is in the form of a solution.

66. (new) A method for treating pain in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 55.